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COMMENT(S)/NOTE(S):

UMO 1561.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Gabor Forgacs, et al. Art Unit 1657
Serial No. 10/590,446
Filed October 10, 2007
Confirmation No. 8467
For Self-Assembling Cell Aggregates and Methods of Making Engineered Tissue Using the Same
Examiner Kailash C. Srivastava

October 4, 2010

DRAFT RESPONSE TO RESTRICTION REQUIREMENT
FOR DISCUSSION PURPOSES ONLY - DO NOT ENTER

FAX # 571-273-0923

DIRECTOR OF THE UNITED STATES PATENT AND
TRADEMARK OFFICE
P.O. Box 1450
Alexandria, Virginia 22313-1450

SIR:

Please consider the remarks concerning the restriction requirement beginning on page 6 below in advance of the telephone interview scheduled for October 5, 2010 at 2 p.m. eastern time. Applicants will want to discuss these remarks during the telephone interview.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 8 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions of claims in the application:

Listing of Claims:

1. *(Original)* A method of producing a plurality of fused aggregates forming a desired three-dimensional structure, the method comprising: depositing a layer of a matrix on a substrate; embedding a plurality of cell aggregates, each comprising a plurality of cells, in the layer of the matrix, the aggregates being arranged in a predetermined pattern; allowing at least one aggregate of said plurality of cell aggregates to fuse with at least one other aggregate of the plurality of cell aggregates to form the desired structure; and separating the structure from the matrix.

2. *(Original)* The method of claim 1 wherein the layer of the matrix constitutes a first layer, the plurality of cell aggregates constitutes a first plurality of cell aggregates, and the predetermined pattern constitutes a first predetermined pattern, the method further comprising the steps of: depositing a second layer of the matrix on the first layer; and embedding a second plurality of cell aggregates in the second layer, the second plurality of cell aggregates comprising a plurality of cells, the second plurality of cell aggregates being arranged in a second predetermined pattern, and allowing at least one cell aggregate in the first plurality of cell aggregates to fuse with at least one cell aggregate in the second plurality of cell aggregates.

3. *(Original)* The method of claim 2 wherein the first and second predetermined patterns are substantially the same, and wherein the second plurality of cell aggregates is embedded in the second layer of the matrix in registration with the first plurality of cell aggregates.

4. *(Original)* The method of claim 2 wherein the desired structure is a tube, the first and second predetermined patterns are both circular in shape, and the second plurality of cell aggregates is embedded in the second layer of the matrix in registration with the first plurality of cell aggregates.

5. *(Original)* The method of claim 1 wherein the thickness of the layer of the matrix is about equal to the average diameter of the plurality of cell aggregates.

6. *(Original)* The method of claim 1 wherein the cell aggregates are substantially spherical.

7. *(Original)* The method of claim 1 wherein the cell aggregates are substantially uniform in size.

8. *(Original)* The method of claim 1 wherein the cell aggregates have an average size between about 100 and about 600 microns.

9. *(Original)* The method of claim 8 wherein no more than about 10% percent of the cell aggregates deviate from said average size by more than 5%.

10. *(Canceled)*

11. *(Original)* The method of claim 1 wherein the cell aggregates consist essentially of cells of a single type.

12. *(Original)* The method of claim 1 wherein at least one of the cell aggregates comprises a plurality of cells of a first type and a plurality of cells of a second type that is different from the first type.

13. *(Original)* The method of claim 12 wherein said at least one cell aggregate comprises a mixture of said cells of the first type and said cells of the second type and the method further comprises the step of allowing at least some of the cells of the first type to segregate from at least some of the cells of the second type.

14. *(Original)* The method of claim 13 wherein the cells of the first type are epithelial cells and the cells of the second type are connective tissue-forming cells.

15. *(Original)* The method of claim 1 wherein the predetermined pattern comprises a ring

16. *(Original)* The method of claim 1 wherein the matrix comprises a gel.

17. *(Original)* The method of claim 1 wherein said plurality of cell aggregates includes at least one cell aggregate consisting essentially of cells of a first type and at least one other cell aggregate consisting essentially of cells of a second type different from the first type.

18-51. *(Canceled)*

52. *(Original)* A three-dimensional layered structure comprising: at least one layer of a biocompatible matrix; and a plurality of cell aggregates, each cell aggregate comprising a plurality of living cells; wherein the cell aggregates are embedded in the at least one layer of biocompatible matrix in a predetermined pattern.

53. *(Original)* The structure of claim 52 wherein the cell aggregates are substantially uniform in size and shape.

54. *(Original)* The structure of claim 52 wherein the cell aggregates are cylindrical.

55. *(Original)* The structure of claim 54 wherein the cylindrical cell aggregates are from about 100 microns to about 600 microns in height.

56. *(Original)* The structure of claim 52 wherein the cell aggregates are substantially spherical.

57. *(Original)* The structure of claim 56 wherein the substantially spherical cell aggregates are between about 100 and about 600 microns in diameter.

58. *(Original)* The structure of claim 52 wherein each cell aggregate comprises a plurality of living cells of a single cell type.

59. *(Original)* The structure of claim 52 wherein each cell aggregate comprises a plurality of living cells of a first cell type and a plurality of living cells of a second cell type, the second cell type being different from the first cell type.

60. *(Original)* The structure of claim 52 wherein the plurality of cell aggregates comprises a plurality of cell aggregates of a first cell type and a plurality of cell aggregates of a second cell type, the second cell type being different from the first cell type.

61. *(Original)* The structure of claim 52 wherein the layer of biocompatible matrix is about

100 microns to about 600 microns thick.

62. *(Original)* The structure of claim 52 wherein the biocompatible matrix is selected from the group consisting of thermo-reversible gels, photo-sensitive gels, pH-sensitive gels, cell type specific gels, and combinations thereof.

63. *(Original)* The structure of claim 52 wherein the at least one layer of biocompatible matrix comprises at least two different types of biocompatible matrices.

64. *(Original)* The structure of claim 52 comprising: a first layer of the biocompatible matrix; and a second layer of the biocompatible matrix deposited on the first layer; wherein the cell aggregates are embedded in the first layer and in the second layer in a predetermined pattern.

65. *(Original)* The structure of claim 64 further comprising at least one additional layer of the biocompatible matrix deposited on the second layer, wherein the cell aggregates are embedded in the first layer, the second layer, and the at least one additional layer in a predetermined pattern.

66. *(Original)* The structure of claim 64 wherein the first layer comprises a type of biocompatible matrix that is different from the type of biocompatible matrix in the second layer.

67-84. *(Cancelled).*

REMARKS

Claims 67-84 are cancelled without prejudice. Applicants attempted to add these claims through a Preliminary Amendment filed August 20, 2010. However, applicants did not know about the Office action issued August 9, 2010 when they filed this Preliminary Amendment. Applicants understand the Preliminary Amendment was entered in so far as it is part of the record. The Examiner has stated to the undersigned that this Preliminary Amendment will not be considered and that this fact will be noted in the next Office action. Applicants are not entirely sure on the basis of the facts recited above whether or not claims 67-84 are actually pending. To avoid confusion, applicants are "cancelling" these claims in this response. Applicants further plan to continue noting the status of claims 67-84 as "cancelled" in any future response and if any new claims are added to this application, applicants plan to start with claim number 85 because applicants believe this will result in the clearest record of the prosecution for this application. If the Examiner believes it would be necessary for applicants to begin numbering any new claims with number 67 to comply with the rule requiring claims to be numbered sequentially, applicants respectfully request the Examiner to provide an instruction to this effect in the next action so unnecessary delays over non-substantive issues can be avoided.

Response to Restriction Requirement

Applicants hereby elect claims **[provisional election will be made in the formal response]** with traverse. It is not proper to apply any restriction requirement to claims 1-9, 11-17, and 52-66 for the reasons set forth below. Accordingly, applicants respectfully request withdrawal of the restriction requirement and substantive examination for claims 1-9, 11-17, and 52-66.

The Office action divides the claims into the following Groups:

Group I, consisting of claims 1, 5-9, and 11-17, which are drawn to a method of producing a plurality of fused cell aggregates forming a desired three dimensional structure by depositing a layer of a matrix on a substrate, embedding a plurality of cell aggregates in the layer according to a predetermined pattern so that when the cell aggregates are allowed to fuse they form the desired structure;

Group II, consisting of claims 2-4, which are drawn to the same method as recited in claim 1 and further specify a second layer of matrix is deposited on the first layer and a second

plurality of cell aggregates are embedded in the second layer according to a predetermined pattern such that when the cell aggregates are allowed to fuse at least one cell aggregated embedded in the first layer is fused with at least one cell aggregate in the second layer to form the desired structure; and

Group III, consisting of claims 52-66, which are drawn to a three-dimensional layered structure comprising at least one layer of a biocompatible matrix and a plurality of cell aggregates embedded in the matrix in a predetermined pattern.

The present application is a national phase application so the restriction practice is governed by the unity of invention provisions of PCT Rule 13, 37 CFR § 1.475, and MPEP 1893.03(d). Rule 1.475(b) states in pertinent part:

> "a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
>
> (1) a product and a process specially adapted for the manufacture of said product . . . " (Emphasis added).

In this case claim 52 claims a product and claim 1 claims a method that includes making the product. Thus, there is unity of invention between claims 1 and 52 pursuant to Rule 1.475(b)(1).

There is also at least one common technical feature for each of claims 1-9, 11-17 and 52-66. See Rule 1.475(a). The technical contributions for the present invention include that applicants are the first to conceive of and enable production of desired three-dimensional engineered tissue structures by embedding a plurality of cell aggregates in a biocompatible matrix according to a predetermined pattern so the cell aggregates will self-assemble into the desired three-dimensional structure. The structural evolution of cells embedded in a matrix depends on several variables including, for example, the adhesive forces between cells, adhesive and cohesive forces between the cells and the matrix, the characteristics of the matrix (including its composition and spatial structure), and the pattern by which cells are arranged in the matrix. The interactions between the matrix and the cells are complex and it is very likely that structural evolution of the cells will not go as planned (i.e., the outcome will be something other than the desired structure) unless a correct combination of process variables is used. For instance, it is possible the cells could be dispersed into multiple undesired structures (e.g., as

illustrated in Fig. 11B of the present application) rather than evolve into the desired structure. As is described in detail in the specification, for example, applicants developed and validated new computer modeling methods adapted to identify combinations of substances used to form the matrix, the particular types of cells and cell aggregates, and embedding patterns that will reliably result in the cell aggregates evolving into the desired structure rather than an undesired structure that cannot be used for the particular application for which the tissue is being engineered.

The prior art cited in the Office action does not disclose or suggest this technical contribution. The Koibuchi article describes an experiment in which single cell aggregates are implanted into different tadpoles at various locations along a developing limb bud and the resulting morphogenesis of the limb structure is observed. Each tadpole receives only one implanted cell aggregate. See end of first paragraph of "Results" section, p. 142. The single cell aggregate is not arranged with other cell aggregates into a predetermined pattern selected to result in a desired tissue construct when the cell aggregates fuse. There is no desired structure in the experiment described in Koibuchi. The object of Koibuchi's experiment is not to produce a desired tissue construct, but to see what happens when the cell aggregate is implanted at different locations. In particular, the objective is to determine where cells from the cell aggregate go in the developing limb in order to better understand processes controlling morphogenesis of the developing limb. Koibuchi does not explain how to embed a plurality of cell aggregates according to an embedding pattern to obtain a desired structure.

Koibuchi also reports implantation of the cell aggregate results in formation of supernumerary structures (i.e., extra digits) in the developed limb in some cases, but not others. See Page 144, left column, Table 1, and Fig. 6D. Koibuchi fails to explain why supernumerary structures result in some cases but not others. Applicants do not believe the limbs with supernumerary structures should be considered desired structures, but even if they are desired for whatever reason, Koibuchi does not explain how to use a predetermined embedding pattern for the cell aggregate to obtain the supernumerary structures. On the other hand, to the extent a normal limb is a desired structure, Koibuchi does not provide any inducement for a person having ordinary skill in the art to implant any cell aggregates into the organism at all. Instead, if the desired structure is a tadpole having a normal limb, the skilled person would simply let nature run its course without implanting any cell aggregate into the developing limb.

Libera (US 20030153078) also fails to disclose or suggest the technical contribution uniting the claims of this application. Libera discloses methods in which cells are cultured under conditions in which they arrange themselves into cell aggregates. Because the cells assemble

themselves into aggregates in culture, the aggregates are not arranged in a predetermined pattern during the culturing process. The cell aggregates are harvested and then injected into diseased or degraded tissue of a living organism, using a hypodermic needle for example. There is no disclosure in Libera of injecting the cell aggregates into the tissue accordingly to any predetermined pattern. Instead, as indicated in paragraphs [0017], [0030], and [0038], the process involves injecting a solution containing 100-200 cell aggregates into the defect. There is no effort to control where any particular cell aggregate is positioned at the defective tissue site relative to any other cell aggregates. Thus, Libera also fails to disclose any predetermined pattern for the cell aggregates.

Because at least the technical contribution of arranging cell aggregates according to a predetermined pattern is not disclosed or suggested in the prior art cited in the Office action and because each of claims 1-9, 11-17, and 52-66 includes this as a common special technical features, it is improper to issue any restriction requirement for these claims pursuant to Rule 1.475(a).

CONCLUSION

The Commissioner is hereby authorized to charge any fees that are required for this response and not otherwise provided to Deposit Account No. 19-1345.

Respectfully submitted,

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KFJ/NCW/bcw